UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/405,920	09/24/1999	SERGE CARILLO	ST94037A-US	1045

29693 7590 01/29/2003

WILEY, REIN & FIELDING, LLP
ATTN: PATENT ADMINISTRATION
1776 K. STREET N.W.
WASHINGTON, DC 20006

EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/405,920	Applicant(s) Carillo
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 21, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *30-41* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *30-41* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *20*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The request filed on 10/21/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/405,920 is acceptable and a CPA has been established. Applicant's amendment and arguments received on 10/21/02 have also been entered. Claims 18-29 have been canceled as requested, and new claims 30-41 have been entered. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of claims 21-22, and 28-29 under 35 U.S.C. 112, first paragraph, for lack of written description of "parts" of calpastatin is withdrawn in view of applicant's cancellation of the claims.

Please note that the rejection has not been maintained over new claims 30-41 in view of the evidence submitted by applicants in the form of the teachings of Carafoli et al. While the Carafoli et al. reference was published after the effective filing date of the instant application, Carafoli et al. does teach and provide references for publications that demonstrate that fragments

of calpastatin which were capable of inhibiting calpain were known in the art prior to applicant's effective filing date of 5/31/94.

The rejection of canceled claims 18-29 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained over new claims 30-41. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons of record as discussed in detail below. Please note that while claims 36-41 are directed to a composition comprising an adenoviral vector, the claims are included in this rejection based on their intended use in intratumoral injection *in vivo* for the treatment of tumors.

The applicant argues that the office has not made a *prima facie* case of lack of enablement substantiated with adequate evidence. The applicant states that the specification correctly describes methods and vectors useful for inhibiting p53 degradation in a cell and that the references provided with the instant response support the enablement of applicant's methods.

In regards to establishing a *prima facie* case of lack of enablement substantiated with adequate evidence, the previous office actions and the instant office action have analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. Please note that case law including the Marzocchi decision sanctions

both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). The references cited as evidence in the previous office actions, Verma et al., Orkin et al., Dachs et al.,and Marshall et al., teach the unpredictability of achieving therapeutic levels of expression of a transgene *in vivo* by either direct or indirect administration of a recombinant vector or cells transduced/transfected with a recombinant vector. The references base their analysis of the state of the art of gene therapy not simply on clinical trial data, but also on data from *in vitro* studies and *in vivo* studies in art accepted animal models. Furthermore, the previous office action pointed out that *In re Brana* states that if a compound exhibits some desirable pharmaceutical property in a standard experimental animal it has made a significant and useful contribution to the art. Such is not the case in the instant application. The specification fails to provide any *in vitro* or *in vivo* data using the disclosed vectors. It is well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). In the instant case, there is no evidence in the specification which supports that vectors including adenoviral vectors encoding a protein capable of inhibiting both wild type or mutant p53 degradation in any type of cell *in vivo* can be readily obtained without undue experimentation. Please note that case law teaches that

while working examples are not required, ".. the lack of working examples, is, nevertheless, a factor to be considered in a case involving both physiological activity and an undeveloped art. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them". *Ex parte Sudilovsky* (BdPatApp&Int) 21 USPQ2d 1702, citing *In re Novak*, 306 F.2d 924, 134 USPQ 335 (CCPA 1962) 4 and *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

Case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves. *In re Gardner* 166 USPQ 138 (CCPA) 1970. The specifications working examples utilize purified calpastatin protein in cell free *in vitro* assays. While the specification provides a working example which discusses the construction of a recombinant adenoviral vector encoding calpastatin, the specification does not provide any data regarding the activity of this vector, its capacity to infect and express calpastatin in any and all cells, and the level of calpastatin produced in the various cell types. Further, the specification does not provide any guidance concerning the level of calpastatin expression that correlates with an effect on p53 degradation in intact cells. The specification also teaches that the disclosed vectors can be administered in vivo for the purpose of increasing levels of p53 in tumor cells, particularly tumor cells with one mutated and one wild type copy of p53, such that apoptosis is induced. The specification fails to provide sufficient guidance as to the level

of calpastatin expression and the level of inhibition of calpain dependant p53 degradation that correlates with increased apoptosis in the presence of mutated p53.

In regards to the references provided with the instant response, it is noted that all of these papers were published several years after the effective filing date of the instant application. The applicant is also reminded that according to *In re Glass*, if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date. *In re Glass*, 181 USPQ 31, (CCPA 1974). Furthermore, none of the references utilize or suggest the use of a adenoviral vector encoding a specific inhibitor of calpain to inhibit protein degradation or change p53 levels in a cell. The references, with the exception of Pariat et al., teach the use of protein or chemical calpain inhibitors. Thus, a nexus between the teachings of these post-filing references and the instant invention cannot be made. In regards to Pariat et al., Pariat teaches that the co-transfection of cell *in vitro* with a plasmid encoding full-length wild type calpastatin and a plasmid encoding p53 results in increased levels of p53 protein in the cells compared to cells transfected with p53 alone. Pariat et al. neither suggests nor demonstrate inhibiting p53 degradation *in vivo* or the treatment of tumors by intratumoral administration of a vector encoding calpastatin. Further, Pariat et al. uses a vector encoding full-length wild type calpastatin, and does not suggest or teach the use of other calpain inhibitors or the use of fragments of calpastatin. Thus, applicant's claims are not commensurate in scope with

the teachings of Pariat et al., which are limited to the transfection of cells *in vitro* with a vector encoding wild type full-length calpastatin.

Thus, in view of the high level of unpredictability in achieving therapeutic levels of gene expression in particular target cells, and the lack of guidance in the specification for the parameters affecting gene delivery, the dosage of transduced cells or recombinant DNA, appropriate promoter/enhancer combinations and the level of calpain inhibitor expression required to achieve an effect on p53 cellular levels, the lack or working examples, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30-35 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. New claim 30 recites a method of inhibiting protein degradation in a cell comprising administering an adenoviral vector comprising a nucleic acid encoding a specific inhibitor of calpain protease activity and detecting a change in the level of p53 protein in the cell or cell extracts. The claim as written is confusing in that it is unclear from the method steps recited whether applicants intend to claim simply a method of inhibiting protein

degradation, or a method of detecting whether the expression of specific inhibitor of calpain protease activity is capable of changing the level of p53 protein in the cell. The "detecting a change in the level of p53 protein" step appears to belong to a method of screening rather than a method of inhibiting protein degradation. It is suggested that applicants amend the claim to recite, "wherein the expression of the inhibitor results in a change in the level of p53 protein in the cell....".

Claims 33 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 33 and 39 recite wherein the nucleic acid comprises a sequence encoding SEQ ID NO:3. According to the sequence listing, SEQ ID NO:3 is a nucleic acid. Thus, the claim is confusing since the term "encoding" refers to an amino acid sequence rather than a nucleic acid sequence. It is suggested that applicants amend the claim to recite, ".. wherein the nucleic acid comprises the sequence of SEQ ID NO:3".

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER